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Thesis Title:

Striatonigral direct pathway activation is sufficient to induce repetitive behaviors

（黒質線条体直接路の活性化は常同行動を引き起こす）

Thesis Summary: fMRI studies in Human with obsessive compulsive disorder (OCD) evidenced an over-activity of the orbitofrontal cortex (OFC) to the ventral striatum (VS) projections. A recent study succeeded the modeling of OCD-like behavior in mice on the basis of clinical evidence; selective and repetitive activation of VS projecting OFC neurons induced a chronic, but not acute, over-grooming, which is relevant to human OCD phenotype (Ahmari et al.,2013). The next challenge of OCD-related circuit genetics was to clarify which cell type is involved in the pathogenesis of OCD-like behaviors. Indeed, VS projecting OFC neurons terminate on two distinct populations, called striatonigral and striatopallidal projection neurons, but which cell type mediates the pathogenesis was still unknown. In my PhD thesis, I hypothesized that the overactivation of striatonigral neurons caused the chronic over-grooming observed in the study presented above. To selectively activate striatonigral neurons, I used transgenic mice in which step function channelrhodopsin2 (ChR2 (C128S)) were expressed by both striatal projection neurons (i.e. D1 receptors expressing medium spiny neurons and D2 receptors expressing medium spiny neurons). Specifically, these mice were obtained by crossing PDE10a2-tTA with tetO-ChR2(C128S) transgenic mice, generating bigenic mice expressing a step-function variant of ChanelRhodopsin in both D1+ and D2+ MSNs. They were implanted in the left posterior Substantia Nigra pars reticulata (AP :-3.40 ML :-0.3 DV :-3.75), with a 200um optic fiber (NA:0.39) 1 week prior to the behavioral experiment. We then inserted an optic fiber onto the left ventral mesencephalon, enabling the selective illumination of striatonigral neurons axon terminals. To assess the effect of the opto-activation of striatonigral neurons, we examined the firing of putative connected neurons in the ventral mesencephalon. Fifty millisecond blue light illumination blocked the firing for over 15 seconds, indicating that optogenetically activated striatonigral neurons released GABA. Five second blue light illumination was given every minute, 5 times per day, for 5 consecutive days and repetitive behaviors were measured. Repeated activation of striatonigral neurons was sufficient to induce chronic abnormal repetitive behaviors, but suprisinlgy, it also induced abnormal repetitive behaviors during the photostimulation, suggesting a causal role played by the direct pathway in the pathogenesis and expression of abnormal repetitive behaviors.

Pharmacological intervention in the substantia nigra is known to induce repetitive behaviors in rodents, but a direct causal relationship between a particular neural circuit and repetitive behavior has not yet been established. Here we demonstrate that acute excitation in dopamine D1 receptor-expressing MSNs terminals in the substantia nigra pars reticulata by optogenetics resulted in sustained and chronic repetitive behaviors. These data show for the first time that activation of the striatonigral direct pathway is sufficient to generate motor stereotypies.